BEST AVAILABLE COPY

U.S. Food and Drug Administration — Department of Health and Human Services

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Search CFR Title 21 Database

Help | More About 21CFR

There are 2 kinds of searches available: Enter a *Part & Section Number*
OR
select a *CFR Part* or a *Full-Text Search*. You may also combine the *CFR Part* and the *Full Text Searches*

Title21 Part.Section *(e.g., 862.1385)*

CFR Title 21 - Food and Drugs: Parts 1 to 1405

(1) General enforcement regulations
(2) General administrative rulings and decisions
(3) Product jurisdiction
(5) Organization
(7) Enforcement policy

Full Text Search:

Enter a single word (e.g., catheter), an exact phrase (e.g., catheter line) or multiple words connected by *and* (e.g., catheter *and* tubing).

Search Regulation(s) Clear

Database Updated April 1, 2004

S/N 10/007,393
Amendment dated Sept 29, 2005
Office Action dated July 13, 2005
Exhibit 1

1 INTRODUCTION

Chapter 1, "Introduction," is an overview of the medical device regulations with general information pertaining to premarket approval.

Products meeting the definition of a medical device under section 201(h) of the Federal Food, Drug and Cosmetic Act (FD&C Act) are regulated by the Food and Drug Administration (FDA). Medical devices are subject to general controls and other controls in the FD&C Act. General controls of the FD&C Act are the baseline requirements that apply to all medical device manufacturers. Unless specifically exempted, medical devices must be properly labeled and packaged, be cleared for marketing by the FDA, meet their labeling claims, and be manufactured in accordance with FDA's Quality Systems (QS) Regulation.

FDA regulates devices to assure their safety and effectiveness. To fulfill provisions of the FD&C Act, FDA develops and promulgates rules to regulate devices intended for human use. These regulations are published in the *Federal Register*. Final regulations are codified annually in the Code of Federal Regulations (CFR). Most medical device regulations are described in Title 21 CFR Parts 800 to 1299.

WHAT IS A MEDICAL DEVICE

The definition of a medical device appears in section 201(h) of the FD&C Act. A device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory, which is recognized in the official National Formulary, or the United States Pharmacopeia (USP), or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

CLASS	REGULATORY CONTROLS
Class I	General Controls
Class II	General Controls and Special Controls
Class III	General Controls and Premarket Approval

GENERAL CONTROLS

As noted above, general controls are the baseline requirements of the FD&C Act that apply to all medical devices. Unless specifically exempted by regulation, general controls contain requirements for device manufacturers or other designated persons to:

- comply with the registration and listing regulations in 21 CFR Part 807;
- comply with the labeling regulation in 21 CFR Part 801, 809 or 812;
- comply with the reporting regulations in 21 CFR Part 803 and 804;
- submit a premarket notification [510(k)] (21 CFR Part 807) to FDA; and
- design and produce devices under the Quality Systems Regulation (21 CFR Part 820).

The controls in the above list other than reporting regulations are briefly described in this chapter.

Registration and Listing

Section 510 of the FD&C Act requires that U.S. device manufacturers and distributors register their establishments with FDA on Form FDA-2891. All manufacturers are required to list the generic type of devices they have in U.S. commerce with FDA on Form FDA-2892. Establishment registration and medical device listing should be submitted prior to commercial distribution.

Labeling

All medical devices in U.S. commerce must be properly labeled. Device labeling requirements of the FD&C Act are found in the following parts of Title 21:

General Device Labeling	21 CFR Part 801
In Vitro Diagnostic Products	21 CFR Part 809

Investigational Device Exemptions	21 CFR Part 812
Quality Systems Regulation	21 CFR Part 820
General Electronic Products	21 CFR Part 1010

Basic labeling requirements and recommended labeling for medical devices can be found in the ODE Blue Book Memorandum, "Device Labeling Guidance," #G91-1 (see Chapter 4), and in the booklet, *Labeling; Regulatory Requirements for Medical Devices*, available from the Division of Small Manufacturers Assistance (DSMA). Details concerning Blue Book memoranda are found in Chapter 4.

Good Manufacturing Practices

As required by section 520(f) of the FD&C Act, the Quality System (QS) regulation covers the methods used for, and the facilities and controls used for, the design, manufacture, labeling, packaging, storage, and installation of devices. The QS regulation is codified in 21 CFR Part 820. Some class I devices, such as an manual surgical instruments for general use, 21 CFR Section 878.4800, are exempt by regulation from most of the QS requirements.

The QS regulation contains general quality assurance (QA) or quality system requirements in areas of concern to all manufacturers of finished devices. Among other requirements, it covers organization and personnel; design practices and procedures; buildings and environmental control; design of labeling and packaging; controls for components, processes, packaging and labeling; finished device evaluation; distribution and installation; device and manufacturing records; complaint processing; and QA system audits.

SPECIAL CONTROLS

In addition to general controls, class II and III devices are subject to further requirements such as special controls and premarket approval, respectively.

Class II devices are defined in section 513(a)(1)(B) of the FD&C Act to include any device for which reasonable assurance of safety and effectiveness can be obtained by applying "special controls". Only general controls will apply to class II devices until special controls are established by regulation(s). Special controls may include special labeling requirements, mandatory performance standards, patient registries and postmarket surveillance.

PREMARKET NOTIFICATION

A premarket notification [510(k)] is a marketing application submitted to FDA to demonstrate that a medical device is as safe and as effective or substantially equivalent to a legally marketed device that was or is currently on the U.S. market and that does not require premarket approval. The premarket notification requirements are found in 21 CFR Part 807, Subpart E.

Most devices are cleared for commercial distribution in the U.S. by the premarket notification [510(k)] process. Most class I devices are exempt from the 510(k) requirement by regulation. However, they are not exempt from other general controls, such as establishment registration and device listing. Before marketing a medical device which is not exempt from the marketing clearance process, the manufacturer must submit a premarket notification [510(k)] or a premarket approval (PMA) application to FDA. The manufacturer cannot market the device in these cases, unless the firm receives a marketing clearance letter from FDA as stated in section 513(i)(1)(A) or section 515(d)(1)(A)(I) of the FD&C Act. Detailed guidance on the 510(k) requirements can be found in the manual, *Premarket Notification 510(k): Regulatory Requirements for Medical Devices.*

INVESTIGATIONAL DEVICE EXEMPTIONS

To allow manufacturers of devices intended solely for investigational use to ship devices for use on human subjects (clinical evaluation), the FD&C Act authorizes FDA to exempt these devices from certain requirements of the Act that would apply to devices in commercial distribution. Clinical evaluation of devices not cleared for marketing, unless exempt, requires an approved investigational device exemption (IDE) either by an institutional review board (IRB) or an IRB and FDA, informed consent for all patients, adequate monitoring and necessary records and reports. These requirements can be found in 21 CFR Parts 50, 56, and 812. Detailed guidance on the IDE requirements can be found in the *Investigational Device Exemption Manual.*

PREMARKET APPROVAL

Premarket approval (PMA) is the FDA process to evaluate the safety and effectiveness of class III devices. Class III is the most stringent regulatory category for medical devices. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act, in order to obtain marketing clearance.

Devices Subject to Premarket Approval

Under section 515 of the FD&C Act, all devices placed into class III by FDA are subject to premarket approval requirements. Premarket approval is the process of scientific and regulatory review to ensure the safety and effectiveness of class III devices. An approved PMA is, in effect, a private license granted to the applicant for marketing a particular medical device. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed. Premarket approval requirements apply differently to preamendments devices, postamendments devices, and transitional class III devices.

Manufacturers of class III preamendments devices, devices that were in commercial distribution before May 28, 1976, are not required to submit a PMA until 30 months after the promulgation of a final classification regulation or until 90 days after the publication of a final regulation requiring the submission of a PMA, whichever period is later. FDA may allow more than 90 days after promulgation of a final rule for submission of a PMA.

A postamendments device is one that was first distributed commercially on or after May 28, 1976. Postamendments devices that FDA determines are substantially equivalent to preamendments class III devices are subject to the same requirements as the preamendments devices. FDA determines substantial equivalence after reviewing an applicant's premarket notification submitted in accordance with section 510(k) of the FD&C Act. Postamendments devices determined by FDA to be not substantially equivalent to either preamendments devices or postamendments devices classified into class I or II are "new" devices and fall automatically into class III. Before such devices can be marketed, they must have an approved premarket approval application or be reclassified into class I or class II.

Class III transitional devices and "new" devices are automatically classified into class III by statute and require premarket approval by FDA before they may be commercially distributed. Applicants may either submit a PMA or a Product Development Protocol (PDP), or they may petition FDA to reclassify the devices into class I or class II. Clinical studies in support of a PMA, a PDP, or a reclassification petition are subject to the Investigational Device Exemption (IDE) regulation.

The PMA requirements are found in 21 CFR Part 814. Not all class III devices require an approved PMA to be marketed at this time. Class III devices that are substantially equivalent to devices legally marketed before May 28, 1976, and do not currently require premarket approval may be marketed through the premarket notification [510(k)] process until FDA publishes a regulation requiring the submission of a premarket approval (PMA) application for those Class III devices.

The PMA Review Process

The review of a premarket approval application is a four-step review process consisting of:

- administrative and limited scientific review by FDA staff to determine completeness (filing review);
- in-depth scientific and regulatory review by appropriate FDA scientific and compliance personnel (in-depth review);
- review and recommendation by the appropriate advisory committee (panel review); and
- an FDA good manufacturing practices (GMP) inspection.